Anemia management in heart failure patients

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Outline

• The Impact of Anemia on the Prognosis of Chronic Heart Failure
• Drug contributing to failure of anemia management in heart failure
• Management of anemia in acute decompensated heart failure
• Management of anemia in chronic heart failure
• Future research
The Impact of Anemia on the Prognosis of Chronic Heart Failure

A Meta-Analysis and Systemic Review

Anemia is associated with an increased risk of mortality and rate of hospitalization for heart failure. Anemia is an independent risk factor for adverse outcomes in patients with CHF.

Congest Heart Fail. 2009;15:123–130
Drug contributing to failure of anemia management in heart failure
Angiotensin-Converting Enzyme Inhibitor as a Risk Factor for the Development of Anemia

SOLVED trail

Enalapril was associated with increased odds of developing anemia at one year. Enalapril was protective of overall mortality after adjusting for incident anemia and in those with prevalent anemia.

The Journal of the American College of Cardiology 9–45:391;2005

Management of anemia in acute decompensated heart failure

Optimum haemoglobin threshold for transfer blood in acute setting of anemia

Hemoglobin 8 to 10 g/dL – Transfusion generally not indicated, but may be considered for some populations (e.g., those with symptomatic anemia, ongoing bleeding, acute coronary syndrome with ischemia, and hematology/oncology patients with severe thrombocytopenia who are at risk of bleeding)

Controversial!!!

Hemoglobin 7-6 g/dl: restrictive transfusion

Hemoglobin <6 g/dl: transfusion recommended

Management of anemia in acute decompensated heart failure

Optimum haemoglobin threshold for transfer blood in acute setting of anaemia

Restrictive versus liberal transfusion strategy for red blood cell transfusion:
Systematic review and Meta-analysis

Mortality

Restrictive transfusion strategies are safe in most clinical settings. Liberal transfusion strategies have not been shown to convey any benefit to patients.

British medical journal 2015;350:h1354
Management of anemia in acute decompensated heart failure

Hypocalcaemia management due to massive blood transfusion

Calcium chloride may be preferable to calcium gluconate in the presence of abnormal liver function, since citrate metabolism is decreased, resulting in slower release of ionized calcium.

If 10 percent calcium gluconate is used, 10 to 20 mL should be given intravenously (into another vein) for each 500 mL of blood infused.

If 10 percent calcium chloride is used, only 2 to 5 mL per 500 mL of blood should be given.

British Journal of Hematology, 135, 634–641

Management of anemia in chronic heart failure

Effects of erythropoiesis-stimulating agents on heart failure patients with anemia: a meta-analysis

Increase in Hg

Advances Interventional Cardiology 2016; 12, 3 (45): 247–253
Management of anemia in chronic heart failure

Effects of erythropoiesis-stimulating agents on heart failure patients with anemia: a meta-analysis

### B. Comparison of LVEF

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>ESAs Mean</th>
<th>ESAs SD</th>
<th>ESAs Total</th>
<th>Control Mean</th>
<th>Control SD</th>
<th>Control Total</th>
<th>Weight N, random, 95% CI</th>
<th>Mean difference N, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kourea 2008</td>
<td>5</td>
<td>5</td>
<td>21</td>
<td>-5</td>
<td>12</td>
<td>20</td>
<td>18.9 (10.00, 26.88)</td>
<td></td>
</tr>
<tr>
<td>Palazuczi 2007</td>
<td>6.6</td>
<td>6.75</td>
<td>26</td>
<td>-5.5</td>
<td>6.05</td>
<td>25</td>
<td>20.9 (8.30, 11.62)</td>
<td></td>
</tr>
<tr>
<td>Parisi 2008</td>
<td>5</td>
<td>6</td>
<td>21</td>
<td>-3</td>
<td>5.5</td>
<td>11</td>
<td>20.4 (8.00, 12.14)</td>
<td></td>
</tr>
<tr>
<td>Silverberg 2001</td>
<td>5.5</td>
<td>12.3</td>
<td>16</td>
<td>-5.4</td>
<td>7.5</td>
<td>16</td>
<td>17.6 (10.90, 14.79)</td>
<td></td>
</tr>
<tr>
<td>van Veldhuizen</td>
<td>0.02</td>
<td>0.91</td>
<td>110</td>
<td>1.27</td>
<td>1.29</td>
<td>55</td>
<td>22.3 (-1.99, -1.67)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>194</td>
<td></td>
<td>127</td>
<td>100.0</td>
<td></td>
<td>6.88 (0.49, 13.28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 47.77, 
$ $\chi^2 = 72.75, df = 4 (p < 0.00001); I^2 = 95%$

Test for overall effect: $Z = 2.11 (p = 0.03)$

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Management of anemia in chronic heart failure

Effects of erythropoiesis-stimulating agents on heart failure patients with anemia: a meta-analysis

### A. Heart failure hospitalizations

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>ESAs Events</th>
<th>ESAs Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight N, random, 95% CI</th>
<th>Odds ratio N, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleland 2005</td>
<td>3</td>
<td>18</td>
<td>0</td>
<td>6</td>
<td>1.9</td>
<td>2.94 (0.13, 65.26)</td>
</tr>
<tr>
<td>Ghali 2008</td>
<td>2.5</td>
<td>162</td>
<td>31</td>
<td>157</td>
<td>25.6</td>
<td>0.74 (0.42, 1.32)</td>
</tr>
<tr>
<td>Kourea 2008</td>
<td>5</td>
<td>21</td>
<td>5</td>
<td>20</td>
<td>6.2</td>
<td>0.50 (0.30, 2.44)</td>
</tr>
<tr>
<td>Marchi 2003</td>
<td>1</td>
<td>16</td>
<td>4</td>
<td>8</td>
<td>2.9</td>
<td>0.07 (0.01, 0.78)</td>
</tr>
<tr>
<td>Palazuczi 2007</td>
<td>4</td>
<td>20</td>
<td>8</td>
<td>18</td>
<td>7.3</td>
<td>0.33 (0.07, 1.31)</td>
</tr>
<tr>
<td>Parisi 2008</td>
<td>2</td>
<td>21</td>
<td>3</td>
<td>11</td>
<td>4.3</td>
<td>0.36 (0.04, 2.03)</td>
</tr>
<tr>
<td>Ronskovski 2007</td>
<td>4</td>
<td>19</td>
<td>9</td>
<td>22</td>
<td>7.6</td>
<td>0.09 (0.00, 1.55)</td>
</tr>
<tr>
<td>Swedberg 2013</td>
<td>3.4</td>
<td>113.6</td>
<td>381</td>
<td>1142</td>
<td>33.1</td>
<td>1.02 (0.85, 1.28)</td>
</tr>
<tr>
<td>van Veldhuizen</td>
<td>0.02</td>
<td>110</td>
<td>4</td>
<td>55</td>
<td>7.3</td>
<td>0.48 (0.12, 2.00)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1549</td>
<td>2464</td>
<td>100.0</td>
<td></td>
<td>0.61 (0.39, 0.94)</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 364

Heterogeneity: $I^2 = 0.14, \chi^2 = 14.68, df = 9 (p = 0.10), I^2 = 89%$

Test for overall effect: $Z = 2.31 (p = 0.02)$

Advances Interventional Cardiology 2016; 12, 3 (45): 247–253
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Effects of erythropoiesis-stimulating agents on heart failure patients with anemia: a meta-analysis

Conclusions: The treatment of anemia with ESA therapy did not reduce the rate of all-cause mortality among patients with heart failure, but ESA therapy made a potential important contribution to patients' symptomatic improvement.

Advances Interventional Cardiology 2016; 12, 3 (45): 247–253

Management of anemia in chronic heart failure

Cerebrovascular event

Annals of Internal Medicine. 2013;159:746-757
Management of anemia in chronic heart failure

Venous thromboembolic

Annals of Internal Medicine. 2013;159:746-757
Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

**Intravenous or oral?**

**Oral Iron**

- Oral iron therapy is relatively inexpensive and widely used
- Oral iron is most frequently given in the form of ferrous (Fe[II]) salts, such as ferrous sulfate

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European Journal of Heart Failure (2015) 17, 248–262

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Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

**Oral Iron**

- Constipation
- Heartburn
- GIT Symptoms: dyspepsia
- Food
- Interaction: Medication

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European Journal of Heart Failure (2015) 17, 248–262
Management of anemia in chronic heart failure
Iron therapy for the treatment of iron deficiency in chronic heart failure

Oral Iron

Difficult balance between maximizing uptake and minimizing gastrointestinal side effects.
*European Journal of Heart Failure (2015) 17, 248–262*

Dosing consideration

The median required dose of iron to achieve iron repletion in iron-deficient patients with heart failure is **1000 mg**

Given that a typical dose of ferrous sulfate is **100–200 mg**/day

Best scenario

**50 day**

Worse scenario

**100 day**

*European Journal of Heart Failure (2015) 17, 248–262*
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**Oral Iron**

**IRONOUT: Oral Iron Therapy for Heart Failure With Reduced Ejection Fraction: Design and Rationale for Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure**

Carried out in 225 patients, investigated the effect of oral iron polysaccharide (150 mg twice daily) compared with matching placebo. IRONOUT HF is an NIH-sponsored multi-center, randomized, double-blinded, placebo-controlled trial, which enrolled patients between September 2014 and November 2015 at 23 U.S. sites.

*Circulatory Heart Failure, 2016 May;9(5)*

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Management of anemia in chronic heart failure
Iron therapy for the treatment of iron deficiency in chronic heart failure

**Oral Iron**

**IRONOUT: Oral Iron Therapy for Heart Failure With Reduced Ejection Fraction: Design and Rationale for Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure**

- The primary endpoint was the change in exercise capacity as measured by peak oxygen consumption from baseline to week 16.

- Secondary endpoints included changes in distance walked in six minutes, oxygen kinetics, ventilator efficiency, and a quality of life score.

Neither primary nor secondary endpoints differed significantly between groups.

*Circulatory Heart Failure, 2016 May;9(5)*
Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Intravenous Iron

A series of I.V iron complexes has been developed which enclose an iron-containing core within a carbohydrate shell, stabilizing the structure and controlling the release of iron.

Management of anemia in chronic heart failure

Iron therapy for the treatment of iron deficiency in chronic heart failure

Intravenous Iron

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: Meta-analysis

- Toblli et al. 2007
- Okonko et al. 2008
- Beck-da-Silva et al. 2013
- Anker et al. 2009
- Ponikowski et al. 2015

European Journal of Heart Failure (2015) 17, 248–262

European Journal of Heart Failure (2016) 18, 786–795
Management of anemia in chronic heart failure
Iron therapy for the treatment of iron deficiency in chronic heart failure

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure:
Meta-analysis

European Journal of Heart Failure (2016) 18, 786–795

HF hospitalization

-European Journal of Heart Failure (2016) 18, 786–795-
Management of anemia in chronic heart failure
Iron therapy for the treatment of iron deficiency in chronic heart failure

Intravenous Iron

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure:
Meta-analysis

The evidence indicates that I.V iron therapy in iron-deficient patients with systolic HF improves outcomes, exercise capacity, quality of life, and alleviates HF symptoms.

European Journal of Heart Failure (2016) 18, 786–795
Future research

The Effects of Intravenous Iron Therapy for Anemia Correction in Patients With Severe Chronic Heart Failure and Concomitant Moderate Chronic Kidney Disease

ClinicalTrials.gov NCT00384657

Estimated Enrollment: 200
Study Start Date: January 2008
Estimated Study Completion Date: June 2021
Estimated Primary Completion Date: December 2019 (Final data collection date for primary outcome measure)

Inclusion Criteria

Persistent severe CHF: left ventricular ejection fraction (echocardiography) less than 40%.

Stable stage 3 chronic kidney disease: estimated GFR between 30-59mL/min/1.73m²

Mild to moderate anemia: hemoglobin levels < 12g/dL

Iron deficiency: absolute (serum ferritin < 100ng/mL) or functional (serum ferritin 100-300ng/mL and transferrin saturation < 20%)
Future research

The Effects of Intravenous Iron Therapy for Anemia Correction in Patients With Severe Chronic Heart Failure and Concomitant Moderate Chronic Kidney Disease

Trial design

Group I (treatment group)
Subjects assigned to this group will receive intravenous iron (ferric sucrose product Venofer® 2%, 5mL/ampoule) in a starting dose of 200mg (2 ampoules) diluted in 150mL 0.9% NaCl solution, over 60 minutes, once a week for the first four administrations, and then every other week until hemoglobin levels reach 12g/dL. Then, iron dose will be adjusted to 1 ampoule at 2-4 weeks interval, as needed to maintain these levels with serum ferritin ≤500ng/mL.

Group II (control group)
Subjects assigned to this group will continue their conventional treatment for CHF as needed, without iron supplementation

Original Primary Outcome Measures

- Percentage of patients achieving target hemoglobin level (>12g/dL) at the end of the study
- Percentage of the patients reaching a better NYHA functional class at the end of the study
- Absolute change in estimated glomerular filtration rate from baseline at the end of the study
Take home message

Anemia in heart failure associated is with an increased risk of mortality and rate of hospitalization

Enalapril was associated with developing anemia at one year

Restrictive transfusion strategies are safe in most clinical settings.

The treatment of anemia with ESA therapy did not reduce the rate of all-cause mortality, but made lead to patients' symptomatic improvement taking into consideration safety profile

Results of current literature indicates that I.V iron therapy HF improves outcomes, exercise capacity, and quality of life
Thank you